REVIEW ARTICLE

Physiology of bone turnover and its application in contemporary maxillofacial surgery. A review

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Abstract

Backround: Bone formation and remodelling appear as normal developmental or healing processes being inducted by several factors as BMPs, biophysical forces and IGF. A local environment consisted of those factors is created and it is responsible for the changes in the direction bone formation-bone resorption. This exact dynamic property of the bone is evaluated and utilized in the reconstructive surgical treatment of craniofacial deformities.

Methods: Data with regard to the physiology of the biological process of bone turn over are initially analysed, followed by the applications of these mechanisms in orthognathic surgery, cleft lip and palate surgery and reconstructive surgery of midfacial deformities, including experimental data after a review of the contemporary international bibliography.

Results-Conclusion: The growing knowledge of bone physiology will influence future surgery techniques and that is going to lead to greater therapeutic capabilities for our patients. Hippokratia 2010; 14 (4): 244-248

Key words: bone turnover, maxillofacial surgery, physiology, review

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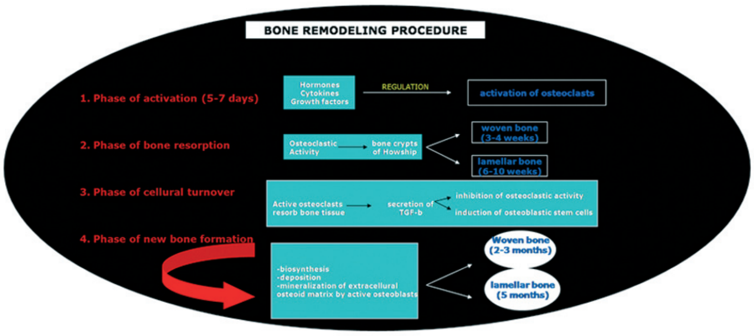
Bone remodeling is a constant and programmed procedure of bone resorption and formation that states the dynamic nature of bone tissue and contributes to the physiologic developmental growth, the retention of human homeostasis and the integration of the healing procedure.

Bone remodeling occurs in four phases[1] (Table 1): 1) Phase of activation. Hormones, cytokines and several growth factors regulate the activation of osteoclasts, 2) Phase of bone resorption. Osteoclastic activity results in the formation of bone crypts of Howship, 3) Phase of cellular turnover. Osteoblastic stem cells proliferate and differentiate into mature and active osteoblasts. Active osteoclasts and resorbed bone tissue induce the secretion of TGF-b1 which is a very important cytokine for the cellular turnover, 4) Phase of new bone formation, including the biosynthesis, deposition and mineralization of the extracellular osteoid matrix that is deposited by active osteoblasts.

Bone remodeling is an essential biological process for craniofacial surgery, especially in cases in which bone regeneration is required for the rehabilitation of bone deformities.

Table 1: Table demonstrating the four phases of bone remodeling procedure.



Distraction osteogenesis is a very efficient method and it is applied in reconstructive surgery during the last years. This method is based on the loading of biophysical forces on bone tissue and was established in orthopedic practice by the pioneering work of Ilizarov[2] who introduced this treatment, followed by McCarthy et al.[3] who used it in Oral and Maxillofacial Surgery.

Distraction osteogenesis is a method of skeletal expansion (bone lengthening) in which the bone is formed in response to tension across an osteotomy. Specifically, distraction osteogenesis is a form of in vivo tissue engineering in which the surgeon, several times after the operation, gradually separates the bone cut and that leads to the generation of new bone.

The advantages of distraction osteogenesis against the traditional use of grafts include[4]: (a) A minimally invasive operation, (b) Elimination of the need for bone grafts thereby avoiding donor site morbidity, (c) The ability to achieve large magnitudes of skeletal expansion, (d) The potential for less relapse because gradual expansion of the surrounding tissue decreases soft tissue resistance. The main disadvantage of this method is that the overall treatment period is longer than the standard techniques of osteotomy, acute bone lengthening and bone grafting[5].

Cleft surgery and orthognathic surgery

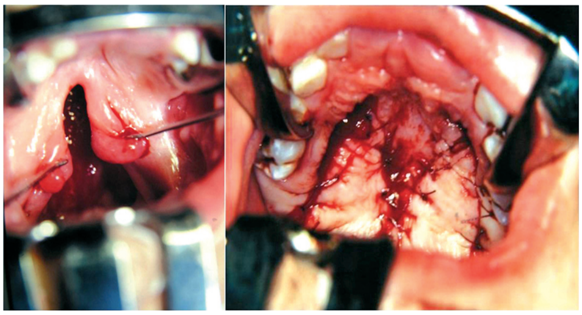


Figure 1: Clinical illustration showing a cleft palate (left) and its reconstruction with push back technique (right).

A large number of protocols have been reported concerning the surgical treatment of cleft lip and palate. Bone formation and remodeling occur both after the primary operation of palatoplasty for the reduction of the palatal deficiency and after the secondary operations including bone grafting, possibly a type of osteotomy and the surgical treatment of some kind of relapse, i.e. oronasal fistulae. The surgical closure of the hard palate (Figure 1) performed at the primary level (usually at 4-5 years of life) substantially substitute the use of a bone graft[6-8]. After the suture of the nasal and the oral mucosa with the palalatoplasty (hard palate), an empty space between those layers remains which is immediately filled by blood clot. The blood clot includes osteoblasts and osteoclasts which induct the bone turn over process. There is a report that the posterior section of the hard palate has little ability for bone formation comparing with the anterior section, which can be explained by the assumption that the posterior part participates at the functions of speech and swelling[9]. Many methods have been described related to the reduction of bone defect in cleft lip and palate which is usually performed at 7-10 years of life, including those who use bone grafts (Figure 2) and those who deal with periosteoplasty. There are advantages and disadvantages in all methods and the bone graft or the periosteum (depending on the method) act like a frame against the infiltration of fibrous tissue in the defect, so inducting the bone formation (inhibit fibrous tissue formation).

In some special cases of cleft lip and palate orthognathic surgery (mainly Le Fort I osteotomy) is very useful. The purpose of osteotomy in such cases is the better alignment and stability of the bony segments during or after the bone transplantation and the various techniques for that purpose include either osteotomy and immobilization (with resorbable or non-resorbable plates and screws)[10] or osteotomy followed by distraction osteogenesis[11]. The main advantage of the distraction osteogenesis is the absence of the need for bone transplantation, however, the disadvantages consist of[12]: a) the unilateral tension produced by the distraction device which will use against the desirable symmetry, b) the difficulty in the anatomical application of the device because of the thin structure of palate c) the need for every day adjustment of dilatator. In 2006 Suzuki et al[13] published a new technique which combines a twin track distraction osteogenesis device with bone transplantation at the same time, promising good results with main advantage the decrease of the number of operations.

The principles mentioned above have validity in the orthognathic surgery for the repair of skeletal abnormalities of maxilla and mandible. In these surgical operations the Le Fort I osteotomy and the sagittal split osteotomy of the mandible prevail. In most cases the osteotomy is followed by immobilization with resorbable or non-resorbable plates and screws (Figure 3) (which replaced the wires used in the past years) and the bone stability remains satisfying with a low rate of collapse. In some cases dealing with large deficiencies, distraction osteogenesis devices are very well applicable, intraorally or extraorally[14,15].

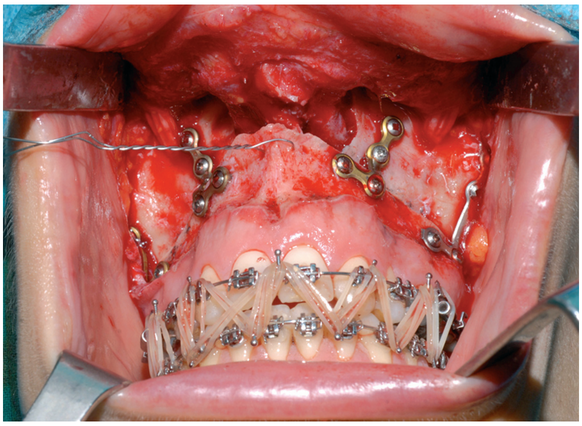


Figure 3: Titanium plates and screws for the immobilization of the segmented maxilla after Le Fort I osteotomy.

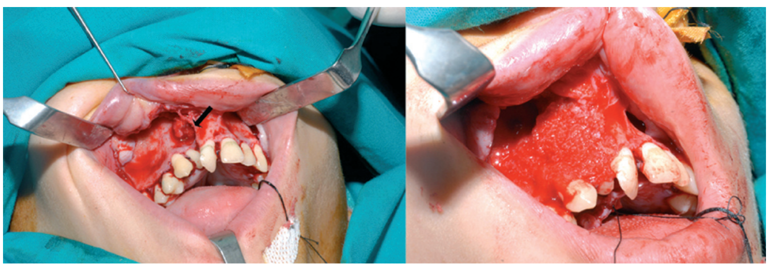


Figure 2: Alveolar bone defect (black arrow) in a cleft patient (left) and its rehabilitation with bone grafting (right). Both bone harvesting from iliac crest of the patient and use of platelet rich plasma (PRP) were carried out so as the defect to be covered.

Preprosthetic surgery

The purpose of preprosthetic surgery is the creation of the appropriate conditions for the better lodgement of classical prosthetic dental appliances or dental implants. A lot of conventional techniques involving bone harvesting

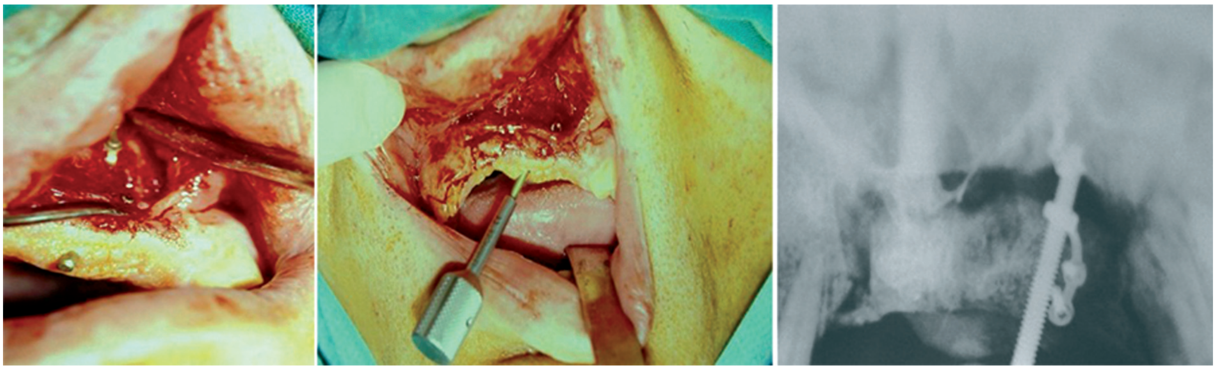


Figure 4: Distraction osteogenesis device lodged at the alveolar patient of a patient (left). The functionality of the device is tested by the operator with a specially designed screwdriver (center). After the end of the tension appliance period, the result is examined radiographicaly.

from intraoral or extraoral sites and the use of allogenic or synthetic bone grafts, have been described for these cases too. During the later years many clinicians have been started using distraction osteogenesis with intraoral (Figure 4)[16,17] or extraoral[18] devices with main advantage the lack of need for the use of a bone graft.

Reconstructive surgery of the midface and surgery of condyle/ramus of the mandible

The Le Fort I, II, III osteotomies are very useful in the treatment of various congenital abnormalities or pathological conditions following accidents concerning the area of midface. The immobilization with wires which was used in the past is replaced nowadays by plates and screws and distraction osteogenesis devices. The role of bone grafts for the stabilization of midface after Le Fort III osteotomy is not clear. The bone grafts which are used for the correction of the disharmony between the supraorbital rims and the forehead tend to resorb. Kaban et al.[19] consider the use of frontofacial advancement instead of C-osteotomy and agree with the use of large organised bone grafts.

In syndromal craniosynostosis, Le Fort III osteotomy is a valuable technique with very good results in the retention after the reduction of the bone deformity[20]. Concerning the influence of Le Fort III osteotomy in the advancement of the mandible, it seems that the osteotomy does not lead to alter the size of mandible despite the midface rotation due to the growth potential[21]. In syndromes which include derivatives of 1st and 2nd brachial arches, i.e. Nager and Hemifacial Microsomia, there is usually the need for reconstruction of the mandible[22]. The difficulties in those cases come from the missing or pathologic muscle insertion and the future advancement of the mandible. As reconstructive techniques distraction osteogenesis devices and cartilage and bone grafts are used and indeed lead to quite good results[23].

Physiology of bone formation after surgery -Discussion

In most studies of mandibular distraction osteogenesis, authors have reported new bone formation by intramembranous ossification[24]. In histological studies of mandibular distraction osteogenesis, it is well documented that new osteoid matrix, woven or lamellar bone formation occurs, despite the different distraction protocols[25]. This deposition occurs within a scaffold of collagen fibers which are oriented parallel to the direction of the distraction. Histologically, three distinct zones can be identified[26]: (1) The zone of original bone ending at the osteotomy margins, (2) The zone of new bone formation between the osteotomy margins and the fibrous inter-zone, (3) The fibrous inter-zone in the center of the wound.

The applied biophysical forces at the osteotomy region include the transduction of mechanical strain, macroscopically, and electromagnetic signals, microscopically, on craniofacial bones at organ, tissue, cellular and molecular levels. Bone has the capacity to be accustomed well to a changing functional environment of the osteotomy. This is referred as phenotype plasticity[27]. At tissue, cellular and molecular levels, the applied distractive forces lead to the deformation of bone tissue that consists of extracellular fluid flow, alter in the ion constitution and change in cellular pressure, oxygen and temperature conditions[28-31]. This procedure leads to the loading of mechanical and electromagnetic stimuli, which induce cellular proliferation, differentiation and secretion of cytokines[32]. Mesenchymal stem cells, emerging from periosteum, proliferate and differentiate into osteoblasts and osteoclasts[33]. Osteoblasts produce and deposit osteoid in the distraction area, differentiate into osteocytes, induce the mineralization of the extracellular matrix, promote the regulation of other cells and the secretion of cytokines that act osteoinductively for the development of bone remodeling[34].

Synthesis and secretion of cytokines and osteoinductive factors play an important role for the development of bone remodeling. Changes in their production, during distraction osteogenesis, is based on the altered synthetic activity of cells in the gap area under mechanical loading. TGF-b1 and IGF-1 are two of the most important cytokines, produced in the distraction gap. Several studies[35-37] report an increase in TGF-b1 concentrations at later stages of distraction osteogenesis and during osteotomy healing. TGF-b1 is a powerful mitogen that stimulates the proliferation of osteoblasts and differentiation of mesenchymal cells into osteoblasts. Meyer et al[37] and Joyce et al[38] report that increased TGF-b1 concentrations are necessary for the bone healing process and for the prevention of fibrous gap tissue local growth, after the mandibular lengthening. IGF-1 concentrations are reduced after the first phase of bone healing. IGF-1 stimulates high bone collagen and DNA synthesis and decreases collagen degradation. The inverse correlation between TGF-b1 and IGF-1 concentration may be responsible for the observation that the mineralization rate is reciprocally related to the serum osteogenic property of the distraction area during bone formation[39].

Bone morphogenetic proteins (BMPs) are a group of endogenous, multifunctional proteins that constitute part of the transforming growth factor beta superfamily. BMPs -2 and -7 are the main osteoinductive factors that are expressed in the osteotomy region[40]. Their concentration increases during the first week of consolidation in the vascularized connective tissue and decreases considerably 14-28 days after distraction. The osteoinductive property of BMPs -2 and -7 occurs at the early stages of distraction and targets upon the undifferentiated mesenchymal cells of the periosteum[41]. Furthermore, it is reported that BMP-2 is strongly expressed at the time of active formation by immature cells[42]. This suggests that BMP-2 has an important role in differentiation from immature mesenchymal cells to bone fibroblasts and osteoblasts. During the last years, there are many well documented studies that report the use of rh-BMP-2 in cases of bone deformities, in order to promote the stronger induction of bone healing and remodeling[43].

The development of the biological process of bone remodeling is strongly associated with the good blood supply (i.e excellent surgical technique so as the vessels of the surgical site not to be damaged) that is required at the osteotomy region. The systemic regulation of angiogenesis in the fibrous inter-zone and later in the newly-formed bone is advanced by the induction of the angiogenic factors VEGF and angiogenin[44,45]. These factors are involved in all steps of angiogenesis, from activation of basement membrane proteases to the construction of endothelial cells to form new blood vessels.

It is obvious that in the future the biological research of the bone will accurately define many unspecified aspects of its physiology. It seems that the revolution generated from the advances of genetics and laboratory sciences will widely influence surgery and enlarge the spectrum of its capabilities. The new generation of surgeons inspired by these advances will create the road of evolution at the field of future reconstructive surgery with newer less invasive surgical techniques.

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